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NEWS 4	APR 28	EMBASE Controlled Term thesaurus enhanced
NEWS 5	APR 28	IMSRESEARCH reloaded with enhancements
NEWS 6	MAY 30	INPAFAMDB now available on STN for patent family searching
NEWS 7	MAY 30	DGENE, PCTGEN, and USGENE enhanced with new homology sequence search option
NEWS 8	JUN 06	EPFULL enhanced with 260,000 English abstracts
NEWS 9	JUN 06	KOREAPAT updated with 41,000 documents
NEWS 10	JUN 13	USPATFULL and USPAT2 updated with 11-character patent numbers for U.S. applications
NEWS 11	JUN 19	CAS REGISTRY includes selected substances from web-based collections
NEWS 12	JUN 25	CA/CAplus and USPAT databases updated with IPC reclassification data
NEWS 13	JUN 30	AEROSPACE enhanced with more than 1 million U.S. patent records
NEWS 14	JUN 30	EMBASE, EMBAL, and LEMBASE updated with additional options to display authors and affiliated organizations
NEWS 15	JUN 30	STN on the Web enhanced with new STN AnaVist Assistant and BLAST plug-in
NEWS 16	JUN 30	STN AnaVist enhanced with database content from EPFULL
NEWS 17	JUL 28	CA/CAplus patent coverage enhanced
NEWS 18	JUL 28	EPFULL enhanced with additional legal status information from the epoline Register
NEWS 19	JUL 28	IFICDB, IFIPAT, and IFIUDB reloaded with enhancements
NEWS 20	JUL 28	STN Viewer performance improved
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NEWS 22	AUG 13	CA/CAplus enhanced with printed Chemical Abstracts page images from 1967-1998
NEWS 23	AUG 15	CAOLD to be discontinued on December 31, 2008
NEWS 24	AUG 15	CAplus currency for Korean patents enhanced
NEWS 25	AUG 25	CA/CAplus, CASREACT, and IFI and USPAT databases enhanced for more flexible patent number searching
NEWS 26	AUG 27	CAS definition of basic patents expanded to ensure comprehensive access to substance and sequence information

NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
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=> s 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine
MISSING OPERATOR '4-(2-FLUOROPH'

=> s 6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine
MISSING OPERATOR '-METHYL-2-(1-PIPERAZI'

=> s 4-2-fluorophenyl-6-methyl-2-1-piperazinylthieno[2,3-D]pyrimidine
      23934093 4
      28573269 2
       1820059 FLUOROPHENYL
      10348393 6
      23033060 METHYL
            98 METHYLS
      23033060 METHYL
               (METHYL OR METHYLS)
      28573269 2
```

```
      25771985 1
             0 PIPERAZINYLTHIENO
        290560 2,3-D
        721233 PYRIMIDINE
L1           0 4-2-FLUOROPHENYL-6-METHYL-2-1-PIPERAZINYLTHIENO[2,3-D]PYRIMIDINE
                 (4(W)2(W)FLUOROPHENYL(W)6(W)METHYL(W)2(W)1(W)PIPERAZINYLTHIENO
                 (W)2,3-D(W)PYRIMIDINE)

=> s 4-2-fluorophenyl-6-methyl-2-1-piperazinylthieno
      23934093 4
      28573269 2
       1820059 FLUOROPHENYL
      10348393 6
      23033060 METHYL
            98 METHYLS
      23033060 METHYL
                 (METHYL OR METHYLS)
      28573269 2
      25771985 1
             0 PIPERAZINYLTHIENO
L2           0 4-2-FLUOROPHENYL-6-METHYL-2-1-PIPERAZINYLTHIENO
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                 )

=> s fluorophenyl-6-methyl-2-1-piperazinylthieno
       1820059 FLUOROPHENYL
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      23033060 METHYL
                 (METHYL OR METHYLS)
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      25771985 1
             0 PIPERAZINYLTHIENO
L3           0 FLUOROPHENYL-6-METHYL-2-1-PIPERAZINYLTHIENO
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=> s mci-224/cn
L4           0 MCI-224/CN

=> s mci-225
            83 MCI
         10757 225
L5           1 MCI-225
                 (MCI(W)225)

=> d l5

L5   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   99487-26-0  REGISTRY
ED   Entered STN:  21 Dec 1985
CN   Thieno[2,3-d]pyrimidine, 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)-,
     hydrochloride (1:1)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Thieno[2,3-d]pyrimidine, 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)-,
     monohydrochloride (9CI)
OTHER NAMES:
CN   MCI 225
DR   135991-48-9
MF   C17 H17 F N4 S . Cl H
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN,
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EMBASE, IMSDRUGNEWS, IMSRESEARCH, MEDLINE, PHAR, PROMT, PROUSDDR,
RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
(*File contains numerically searchable property data)
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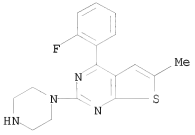

● HCl

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

20 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
20 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> s Thieno[2,3-d]pyrimidine, 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)/cn
MISSING OPERATOR '4-(2-FLUOROPH'

=> s Thieno[2,3-d]pyrimidine, 4-2-fluorophenyl-6-methyl-2-(1-piperazinyl)/cn
MISSING OPERATOR '-METHYL-2-(1-PIPERAZI'

=> s Thieno[2,3-d]pyrimidine, 4-2-fluorophenyl-6-methyl-2-1-piperazinyl/cn
L6 0 THIENO[2,3-D]PYRIMIDINE, 4-2-FLUOROPHENYL-6-METHYL-2-1-PIPERAZIN
YL/CN

=> s 4-2-fluorophenyl-6-methyl-2-1-piperazinyl/cn
L7 0 4-2-FLUOROPHENYL-6-METHYL-2-1-PIPERAZINYL/CN

=> s 4-2-fluorophenyl-6-methyl-2-1-piperazinyl
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28573269 2
1820059 FLUOROPHENYL
10348393 6
23033060 METHYL
98 METHYLS
23033060 METHYL
(METHYL OR METHYLS)
28573269 2
25771985 1
775837 PIPERAZINYL
L8 4 4-2-FLUOROPHENYL-6-METHYL-2-1-PIPERAZINYL
(4(W)2(W)FLUOROPHENYL(W)6(W)METHYL(W)2(W)1(W)PIPERAZINYL)

=> s 4-2-fluorophenyl-6-methyl-2-1-piperazinyl Thieno[2,3-d]pyrimidine
23934093 4

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      28573269 2
       1820059 FLUOROPHENYL
      10348393 6
      23033060 METHYL
            98 METHYLS
      23033060 METHYL
                 (METHYL OR METHYLS)
      28573269 2
      25771985 1
        775837 PIPERAZINYL
        388890 THIENO
        290560 2,3-D
        721233 PYRIMIDINE
L9           0 4-2-FLUOROPHENYL-6-METHYL-2-1-PIPERAZINYL THIENO[2,3-D]PYRIMIDIN
                E
                  (4(W)2(W)FLUOROPHENYL(W)6(W)METHYL(W)2(W)1(W)PIPERAZINYL(W)THI
                  ENO(W)2,3-D(W)PYRIMIDINE)

=> s mci-225/cn
L10          0 MCI-225/CN

=> s mci 225/cn
L11          1 MCI 225/CN

=> d l11

L11  ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2008 ACS on STN
RN   99487-26-0  REGISTRY
ED   Entered STN:  21 Dec 1985
CN   Thieno[2,3-d]pyrimidine, 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)-,
     hydrochloride (1:1)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Thieno[2,3-d]pyrimidine, 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)-,
     monohydrochloride (9CI)
OTHER NAMES:
CN   MCI 225
DR   135991-48-9
MF   C17 H17 F N4 S . Cl H
SR   CA
LC   STN Files:   ADISINSIGHT, BIOSIS, BIOTECHNO, CA, CAPLUS, CHEMCATS, CIN,
       EMBASE, IMSDRUGNEWS, IMSRESEARCH, MEDLINE, PHAR, PROMT, PROUSDDR,
       RTECS*, SCISEARCH, SYNTHLINE, TOXCENTER, USPAT2, USPATFULL
         (*File contains numerically searchable property data)
CRN  (99487-25-9)
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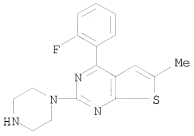

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2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
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=> file medicine
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CA INDEXING COPYRIGHT (C) 2008 AMERICAN CHEMICAL SOCIETY (ACS)

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L12        103 L11

=> s l12 and bowel
L13         24 L12 AND BOWEL

=> dup rem l13
DUPLICATE IS NOT AVAILABLE IN 'ADISINSIGHT, ADISNEWS, DGENE, DRUGMONOG2,
IMSPRODUCT, KOSMET, NUTRACEUT, PCTGEN, PHARMAML, USGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L13
L14          20 DUP REM L13 (4 DUPLICATES REMOVED)

=> d l14 bib abs kwic 1-20

L14  ANSWER 1 OF 20  IMSDRUGNEWS COPYRIGHT 2008 IMSWORLD on STN

AN   2008:523  IMSDRUGNEWS
TI   DDP 225 Arachnova, Dynogen sign asset purchase agreement
SO   R&D Focus Drug News  (28 Jan 2008).
WC   137
TX   Dynogen . . . These patents, which include granted and pending
     applications relating to the use of the agent for the treatment of
     functional bowel disorders, genitourinary disorders and pain,
     complement and extend Dynogen's existing patent estate for DDP 225.
```

Financial terms were not disclosed.

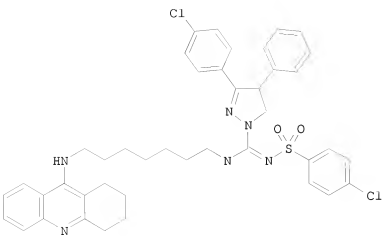
DDP . . . oral noradrenaline reuptake inhibitor and 5HT3 receptor antagonist, has been evaluated in phase II trials for the treatment of irritable bowel syndrome with diarrhea, and the company expects to conduct a phase IIb trial in 2008. In October 2003, Dynogen licensed. . .

RN 135991-48-9
RN 135991-48-9

L14 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2008:771031 CAPLUS
DN 149:104693
TI Compounds with a combination of cannabinoid-CB1 antagonism and acetylcholinesterase inhibition and their preparation
IN Lange, Josephus H. M.; Kruse, Cornelis G.; Shadid, Belal
PA Solvay Pharmaceuticals B.V., Neth.
SO PCT Int. Appl., 48pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2008074816	A1	20080626	WO 2007-EP64169	20071219
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
	RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	US 20080153867	A1	20080626	US 2007-957948	20071217
PRAI	EP 2006-126584	A	20061220		
	US 2006-875808P	P	20061220		

OS MARPAT 149:104693
GI



II

AB This invention concerns compds. of formula I [I = A-(T)n-B, wherein A is essential structural element of known CB1 antagonist; T is a (un)saturated linear carbon liner; B is essential structural element of known acetylcholinesterase inhibitor; N is 0 and 1] with a combination of cannabinoid-CB1 antagonism and cholinesterase inhibition, to pharmaceutical compns. containing these compds., to methods for preparing the compds., methods for preparing intermediates useful for their synthesis, and methods for preparing compns. The invention also relates to the uses of such compds. and compns., particularly for treating Alzheimer's disease, cognitive disorders, memory disorders, dementia, attention deficits, traumatic brain injury, drug dependence, addiction and substance abuse. Compds. of formula II was prepared by a multistep procedure (procedure given). All the invention compds. were evaluated for their CB1 antagonistic activity and their acetylcholinesterase inhibitory activity.

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

IT Intestine, disease
(irritable bowel syndrome, treatment of; preparation of compds. with both CB1 receptor antagonistic and acetylcholinesterase inhibiting activities)

IT 52-68-6DP, Metrifonate, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 55-91-4DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 56-38-2DP, Parathion, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 57-47-6DP, Physostigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 59-99-4DP, Neostigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 87-52-5DP, Gramine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 91-56-5DP, Isatin, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 115-79-7DP, Ambenonium chloride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 116-38-1DP, Edrophonium chloride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 121-75-5DP, Malathion, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 122-14-5DP, Fenitrothion, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 155-97-5DP, Pyridostigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 311-45-5DP, Paraoxon, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 321-64-2DP, Tacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 333-41-5DP, Diazinon, pharmacophoric element, conjugates with

CB1 antagonist pharmacophoric element 357-70-0DP, Galantamine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 402-40-4DP, BW-284-C-51, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 469-22-7DP, (-)-Eseroline, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 495-59-0DP, Desoxypeganine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 558-25-8DP, Methanesulfonyl fluoride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 827-61-2DP, Aceclidine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1563-66-2DP, Carbofuran, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 2258-01-7DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 5778-80-3DP, 7-Methoxytacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 13012-66-3DP, AS-1397, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 15585-43-0DP, Rivanicline, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 19982-08-2DP, Memantine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 21466-07-9DP, Bromophenophos, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 31431-39-7DP, Mebendazole, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 62732-44-9DP, Ipidacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 67909-49-3DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 68497-62-1DP, Pramiracetam, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 81424-67-1DP, Caracemide, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 84371-65-3DP, Mifepristone, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 90043-86-0DP, Amiridine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 96946-42-8DP, Cisatracurium besylate, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 99487-26-0DP, MCI-225, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 101246-66-6DP, (-)-Phenserine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 101246-68-8DP, Eptastigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 102518-79-6DP, Huperzine A, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 117427-00-6DP, ONO-1603, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 120014-06-4DP, Donepezil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 122898-67-3DP, Itopride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 123060-44-6DP, Hoe-065, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 123441-03-2DP, Rivastigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 123690-78-8DP, SGS-742, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 124027-47-0DP, Velnacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 129297-21-8DP, SM-10888, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 132236-18-1DP, Zifrosilone, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 133920-70-4DP, FK-960, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 134959-50-5DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 135017-85-5DP, KW-5092, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 138472-18-1DP, S-9977, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 139314-01-5DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 139886-32-1DP, Milameline, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 142852-50-4DP, Zanapezil,

pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 145209-30-9DP, Tolserine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 145508-78-7DP, Icopezil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 147340-43-0DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 147606-23-3DP, CHF-2060, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 149028-28-4DP, CI 1002, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 149929-39-5DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 154619-51-9DP, MF-268, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 155773-59-4DP, KA-672, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 158182-74-2DP, Ro-46-5934, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 158836-71-6DP, Nitroflurbiprofen, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 164178-33-0DP, AM 630, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 164723-36-8DP, P-11012, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 164724-79-2DP, P-11149, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 168273-06-1DP, Rimonabant, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 176977-56-3DP, LY-320135, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 180694-97-7DP, ZT-1, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 183232-66-8DP, AM 251, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 185104-11-4DP, Z-338, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 188240-59-7DP, P-10358, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 188396-77-2DP, Paliroden, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 191612-12-1DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 192755-52-5DP, Pralnacasan, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 209394-27-4DP, Ladostigil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 219920-81-7DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 223586-00-3DP, CHF-2957, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 223586-01-4DP, CHF-2822, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 224445-12-9DP, Bis-(7)-tacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 252264-92-9DP, T-82, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 263248-16-4DP, TAK-802, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 288104-79-0DP, SR-147778, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 290308-82-6DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 312494-20-5DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 358970-97-5DP, AVE-1625, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 402842-81-3DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 439080-01-0DP, O-2093, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 457075-21-7DP, Ganstigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 464213-10-3DP, SLV319, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 502486-89-7DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 616885-87-1DP, Memoquin, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 686347-12-6DP,

CP-945598, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 701977-09-5DP, MK-0364, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 737738-60-2DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 843660-68-4DP, RS 1439, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 844665-35-6DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 847069-98-1DP, Win 54461, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 847069-99-2DP, SR 140098, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 847796-21-8DP, INM 176, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 848442-09-1DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 864021-55-6DP, EN-101, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 895155-26-7DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 926929-82-0DP, LY-2077855, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 942063-86-7DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 1000202-35-6DP, F 3796, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-38-9DP, FR 152558, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-66-3DP, UR 1827, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-67-4DP, P 11467, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-71-0DP, BGC 20-1259, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-78-7DP, NP 7557, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of compds. with both CB1 receptor antagonistic and acetylcholinesterase inhibiting activities)

L14 ANSWER 3 OF 20 USPATFULL on STN
AN 2008:175983 USPATFULL
TI COMPOUNDS WITH A COMBINATION OF CANNABINOID-CB1 ANTAGONISM AND ACETYLCHOLINESTERASE INHIBITION
IN Lange, Josephus H.M., Weesp, NETHERLANDS
Kruse, Cornelis G., Weesp, NETHERLANDS
Shadid, Belal, Weesp, NETHERLANDS
PA Solvay Pharmaceuticals B.V. (non-U.S. corporation)
PI US 20080153867 A1 20080626
AI US 2007-957948 A1 20071217 (11)
PRAI US 2006-875808P 20061220 (60)
DT Utility
FS APPLICATION
LREP FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP, 901 NEW YORK AVENUE, NW, WASHINGTON, DC, 20001-4413, US
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1612
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Embodiments of this invention relate to compounds having a combination of cannabinoid-CB.sub.1 antagonism and cholinesterase inhibition, to pharmaceutical compositions comprising these compounds, to methods for preparing these compounds, methods for preparing novel intermediates useful for the synthesis of these compounds, and methods for preparing compositions comprising these compounds. The invention also relates to

methods of treating Alzheimer's disease, cognitive disorders, memory disorders, dementia, attention deficit disorder, traumatic brain injury, drug dependence, addiction or substance abuse by administering a pharmaceutical composition comprising these compounds to a patient in need thereof. A compound with a combination of cannabinoid-CB.sub.1 antagonism and cholinesterase inhibition is a compound of formula (1)

##STR1##

wherein the symbols have the meanings given in the specification.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . amnesia, arthritis, cancer, central nervous system disease, cognitive disorder, constipation, dementia, dyspepsia, gastric motility disorder, gastrointestinal disease, gastroparesis, glaucoma, irritable bowel syndrome, major depressive disorder, migraine, multiple sclerosis, muscle disease, muscular dystrophy, myasthenia gravis, neurodegenerative disease, neuropathic pain, nicotine dependence, Pediculus. . .

SUMM . . . dependence, dyspepsia, dystonia, emesis, epilepsy, gastric motility disorder, gastric ulcers, gastrointestinal disorders, gastroparesis, glaucoma, Huntington's disease, impulse control disorders, irritable bowel syndrome, memory disorders, migraine, multiple sclerosis, muscle disease, muscular dystrophy, muscle spasticity, myasthenia gravis, nausea, neurodegenerative disorders, neuroinflammatory disorders, neuropathic. . .

DETD . . . dependence, dyspepsia, dystonia, emesis, epilepsy, gastric motility disorder, gastric ulcers, gastrointestinal disorders, gastroparesis, glaucoma, Huntington's disease, impulse control disorders, irritable bowel syndrome, memory disorders, migraine, multiple sclerosis, muscle disease, muscular dystrophy, muscle spasticity, myasthenia gravis, nausea, neurodegenerative disorders, neuroinflammatory disorders, neuropathic. . .

CLM What is claimed is:

. . . dependence, dyspepsia, dystonia, emesis, epilepsy, gastric motility disorder, gastric ulcers, gastrointestinal disorders, gastroparesis, glaucoma, Huntington's disease, impulse control disorders, irritable bowel syndrome, memory disorders, migraine, multiple sclerosis, muscle disease, muscular dystrophy, muscle spasticity, myasthenia gravis, nausea, neurodegenerative disorders, neuroinflammatory disorders, neuropathic. . .

IT 52-68-6DP, Metrifonate, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 55-91-4DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 56-38-2DP, Parathion, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 57-47-6DP, Physostigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 59-99-4DP, Neostigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 87-52-5DP, Gramine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 91-56-5DP, Isatin, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 115-79-7DP, Ambenonium chloride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 116-38-1DP, Edrophonium chloride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 121-75-5DP, Malathion, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 122-14-5DP, Fenitrothion, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 155-97-5DP, Pyridostigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 311-45-5DP, Paraoxon, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 321-64-2DP, Tacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric

element 333-41-5DP, Diazinon, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 357-70-0DP, Galantamine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 402-40-4DP, BW-284-C-51, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 469-22-7DP, (-)-Eseroline, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 495-59-0DP, Desoxypeganine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 558-25-8DP, Methanesulfonyl fluoride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 827-61-2DP, Aceclidine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1563-66-2DP, Carbofuran, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 2258-01-7DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 5778-80-3DP, 7-Methoxytacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 13012-66-3DP, AS-1397, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 15585-43-0DP, Rivanicline, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 19982-08-2DP, Memantine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 21466-07-9DP, Bromophenophos, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 31431-39-7DP, Mebendazole, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 62732-44-9DP, Ipidacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 67909-49-3DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 68497-62-1DP, Pramiracetam, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 81424-67-1DP, Caracemide, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 84371-65-3DP, Mifepristone, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 90043-86-0DP, Amiridine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 96946-42-8DP, Cisatracurium besylate, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 99487-26-0DP, MCI-225, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 101246-66-6DP, (-)-Phenserine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 101246-68-8DP, Eptastigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 102518-79-6DP, Huperzine A, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 117427-00-6DP, ONO-1603, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 120014-06-4DP, Donepezil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 122898-67-3DP, Itopride, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 123060-44-6DP, Hoe-065, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 123441-03-2DP, Rivastigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 123690-78-8DP, SGS-742, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 124027-47-0DP, Velnacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 129297-21-8DP, SM-10888, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 132236-18-1DP, Zifrosilone, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 133920-70-4DP, FK-960, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 134959-50-5DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 135017-85-5DP, KW-5092, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 138472-18-1DP, S-9977, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 139314-01-5DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 139886-32-1DP, Milameline, pharmacophoric element, conjugates

with CB1 antagonist pharmacophoric element 142852-50-4DP, Zanapezil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 145209-30-9DP, Tolserine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 145508-78-7DP, Icopezil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 147340-43-0DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 147606-23-3DP, CHF-2060, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 149028-28-4DP, CI 1002, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 149929-39-5DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 154619-51-9DP, MF-268, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 155773-59-4DP, KA-672, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 158182-74-2DP, Ro-46-5934, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 158836-71-6DP, Nitroflurbiprofen, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 164178-33-0DP, AM 630, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 164723-36-8DP, P-11012, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 164724-79-2DP, P-11149, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 168273-06-1DP, Rimonabant, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 176977-56-3DP, LY-320135, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 180694-97-7DP, ZT-1, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 183232-66-8DP, AM 251, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 185104-11-4DP, Z-338, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 188240-59-7DP, P-10358, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 188396-77-2DP, Paliroden, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 191612-12-1DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 192755-52-5DP, Pralnacasan, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 209394-27-4DP, Ladostigil, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 219920-81-7DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 223586-00-3DP, CHF-2957, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 223586-01-4DP, CHF-2822, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 224445-12-9DP, Bis-(7)-tacrine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 252264-92-9DP, T-82, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 263248-16-4DP, TAK-802, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 288104-79-0DP, SR-147778, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 290308-82-6DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 312494-20-5DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 358970-97-5DP, AVE-1625, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 402842-81-3DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 439080-01-0DP, O-2093, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 457075-21-7DP, Ganstigmine, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 464213-10-3DP, SLV319, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 502486-89-7DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 616885-87-1DP,

Memoquin, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 686347-12-6DP, CP-945598, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 701977-09-5DP, MK-0364, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 737738-60-2DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 843660-68-4DP, RS 1439, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 844665-35-6DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 847069-98-1DP, Win 54461, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 847069-99-2DP, SR 140098, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 847796-21-8DP, INM 176, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 848442-09-1DP, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 864021-55-6DP, EN-101, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 895155-26-7DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 926929-82-0DP, LY-2077855, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 942063-86-7DP, pharmacophoric element, conjugates with acetylcholinesterase inhibitor pharmacophoric element 1000202-35-6DP, F 3796, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-38-9DP, FR 152558, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-66-3DP, UR 1827, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-67-4DP, P 11467, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-71-0DP, BGC 20-1259, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element 1000202-78-7DP, NP 7557, pharmacophoric element, conjugates with CB1 antagonist pharmacophoric element
(preparation of compds. with both CB1 receptor antagonistic and acetylcholinesterase inhibiting activities)

L14 ANSWER 4 OF 20 IMSDRUGNEWS COPYRIGHT 2008 IMSWORLD on STN

AN 2007:1500 IMSDRUGNEWS
TI DDP 225 Dynogen partnering opportunity, Worldwide
SO R&D Focus Drug News (26 Mar 2007).
WC 112
TX In . . . noradrenaline reuptake inhibitor and 5HT3 receptor antagonist. A multicenter phase II trial of the agent in patients with diarrhea-predominant irritable bowel syndrome (IBS) is under way in Canada, and results are expected second half 2007. Based on these results, Dynogen will. . .
RN 135991-48-9

L14 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 1
AN 2007:1243410 CAPLUS
DN 147:491675
TI Crystalline forms of 4-(2-fluorophenyl)-6-methyl-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine for dosage forms
IN Cooper, Martin Ian; Frampton, Christopher Stephen
PA Dynogen Pharmaceuticals, Inc., USA
SO U.S. Pat. Appl. Publ., 49pp.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI US 20070254891 A1 20071101 US 2007-728947 20070327
WO 2008051282 A2 20080502 WO 2007-US7816 20070327
WO 2008051282 A3 20080731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA
PRAI US 2006-788338P P 20060331
US 2006-808603P P 20060526
AB The present invention is directed to novel crystalline forms of 4-(2-fluorophenyl)-6-methyl-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine salts, including 4-(2-fluorophenyl)-6-methyl-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine hydrochloride (MCI-225) crystalline forms. The present invention is also directed to compns. including such crystalline forms and methods for making and using such crystalline forms, e.g., in the treatment of gastrointestinal and/or genitourinary disorders. Thus, maturation study of MCI-225 was carried out using a diverse set of 25 solvents chosen based on their dielec. constant, dipole moment and functionality. In general, the neat solvents gave Form II and the solvents with 5% water added gave Form I of MCI-225. However, there were one or two exceptions. In neat hexane, toluene, cumene and tetraline, measurements showed either Form I alone or a mixture with Form II. Without wishing to be bound by any particular theory, it is believed that this may be due to low or very low solubility of the compound in these solvents. In isopropanol (IPA), NMP, MeOH, DMF and DMSO with 5% water, measurements showed only Form II. These materials were generally highly crystalline and most were suitable for single crystal work. Again, without wishing to be bound by any particular theory, it is believed that, because Form I is a 1:1 hydrate, solns. with a higher activity of water will have a greater tendency to produce Form I. Also, MCI-225 caused a significant dose-dependent increase in bladder capacity following acetic acid irritation in cats, with individual dose significance attained at the 30 mg/kg dose. These data supported the initial pos. findings in the rat, demonstrating that MCI-225 was effective in increasing bladder capacity in commonly utilized models of overactive bladder in two species. These results were also predictive of the efficacy of MCI-225 in the treatment of benign prostatic hyperplasia (BPH), for example, the irritative symptoms of BPH.
IT Intestine, disease
(irritable bowel syndrome; stable crystalline forms of 4-(2-fluorophenyl)-6-Me-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine salts for dosage forms and treatment of gastrointestinal and urogenital disorders)
IT 99487-25-9D, salts 99487-26-0, MCI-225
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(stable crystalline forms of 4-(2-fluorophenyl)-6-Me-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine salts for dosage forms)

L14 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2007:1204654 CAPLUS
DN 147:462326
TI Soluble salts of thieno[2,3-d]pyrimidine derivatives, and therapeutic use
IN Cooper, Martin Ian
PA Dynogen Pharmaceuticals, Inc., USA

SO PCT Int. Appl., 80pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2007120445	A1	20071025	WO 2007-US7633	20070327

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

US 20070254899	A1	20071101	US 2007-728966	20070327
PRAI US 2006-788565P	P	20060331		
US 2006-808905P	P	20060526		

OS MARPAT 147:462326
AB The invention discloses salts of thieno[2,3-d]pyrimidine derivs., including 4-(2-fluorophenyl)-6-methyl-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine salts. The invention also discloses compns. including such polymorphs and methods for using such salts, e.g., in the treatment of gastrointestinal and/or genitourinary disorders.
RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT
IT Intestine, disease
(functional bowel disorder; soluble salts of thienopyrimidine derivs., and therapeutic use)
IT Diarrhea
(irritable bowel syndrome with; soluble salts of thienopyrimidine derivs., and therapeutic use)
IT Intestine, disease
(irritable bowel syndrome; soluble salts of thienopyrimidine derivs., and therapeutic use)
IT 99487-26-0, MCI-225
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(soluble salts of thienopyrimidine derivs., and therapeutic use)

L14 ANSWER 7 OF 20 USPATFULL on STN
AN 2007:291200 USPATFULL
TI Soluble salts of thieno[2,3-d]pyrimidine derivatives
IN Cooper, Martin Ian, Cambridgeshire, UNITED KINGDOM
Frampton, Christopher Stephen, Suffolk, UNITED KINGDOM
PA Dynogen Pharmaceuticals, Inc., Waltham, MA, UNITED STATES, 02451 (U.S. corporation)

PI	US 20070254899	A1	20071101
AI	US 2007-728966	A1	20070327 (11)
PRAI	US 2006-788565P		20060331 (60)
	US 2006-808905P		20060526 (60)

DT Utility
FS APPLICATION
LREP LAHIVE & COCKFIELD, LLP, ONE POST OFFICE SQUARE, BOSTON, MA, 02109-2127, US
CLMN Number of Claims: 19

ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 2940
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed to novel salts of thieno[2,3-d]pyrimidine derivatives, including 4-(2-fluorophenyl)-6-methyl-2-(piperazin-1-yl)thieno[2,3-d]pyrimidine salts. The present invention is also directed to compositions including such polymorphs and methods for using such salts, e.g., in the treatment of gastrointestinal and/or genitourinary disorders.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . e.g., for the treatment of lower urinary tract disorders (see, e.g., U.S. Pat. No. 6,846,823), for the treatment of functional bowel disorders (see, e.g., U.S. Patent Application Publication No. 2005/0032780), as well as for the treatment of nausea, vomiting, and/or retching. . .
SUMM . . . or genitourinary disorders described herein. For example, gastrointestinal tract disorders or genitourinary disorders include, but are not limited to functional bowel disorders, irritable bowel syndrome, irritable bowel syndrome with diarrhea, chronic functional vomiting, overactive bladder or any combination thereof.
DETD . . . any of the genitourinary disorders described herein. For example, the disorder can be, but is not limited to, a functional bowel disorder, irritable bowel syndrome, irritable bowel syndrome with diarrhea, chronic functional vomiting, overactive bladder, or any combination thereof. It is to be understood that treatment of. . .
DETD . . . been characterized as structural (or mucosal) GI tract disorders and non-structural (or non-mucosal) GI tract disorders. Structural disorders include inflammatory bowel disorders and non-inflammatory structural GI tract disorders. Non-structural disorders include a variety of disorders classified as functional GI tract disorders.
DETD By "inflammatory bowel disorder" is intended any disorder primarily associated with inflammation of the small and/or large intestine, including but not limited to. . . associated with seronegative arthropathies, microscopic or collagenous colitis, eosinophilic gastroenteritis, or pouchitis resulting after proctocolectomy, and post ileoanal anastomosis. Inflammatory bowel disorders include a group of disorders that can cause inflammation or ulceration of the GI tract. Ulcerative colitis and Crohn's disease are the most common types of inflammatory bowel disorders, although collagenous colitis, lymphocytic (microscopic) colitis, and other disorders have also been described.
DETD . . . refer to any disorder primarily associated with altered sensititivity to gluten or gluten byproducts, with or without alterations in small bowel morphology (typically villus blunting) and encompasses all synonyms including celiac sprue and non-tropical sprue. Patients diagnosed with celiac disease may. . .
DETD . . . a chronic inflammatory disorder of unknown etiology afflicting the large intestine and, except when very severe, is limited to the bowel mucosa. The course of this disorder may be continuous or relapsing and may be mild or severe. Medical treatment primarily. . .
DETD . . . structural damage or in the absence of a metabolic disorder. Functional GI tract disorders include functional dysphagia, non-ulcer dyspepsia, irritable bowel syndrome (IBS), slow-transit constipation and evacuation disorders. (Camilleri (2002) Gastrointestinal Motility Disorders, In WebMD Scientific American Medicine, edited by David. . .
DETD In some embodiments, the functional GI tract disorder is a Functional

Bowel Disorder. Functional Bowel Disorders (FBDs) are functional gastrointestinal disorders having symptoms attributable to the mid or lower gastrointestinal tract. FBDs can include, but are not limited to, Irritable Bowel Syndrome (IBS), functional abdominal bloating, functional constipation and functional diarrhea (see, for example, Thompson et al., Gut, 45 (Suppl. II):II43-1147. . .

DETD . . . invention are useful for all manifestations, in some embodiments, the compounds of the present invention are useful in slowing functional bowel. Such compounds would be particularly effective for IBS-d.

DETD As such, IBS is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit. Therefore, IBS has elements of an intestinal motility disorder, a visceral sensation disorder, and a central nervous disorder. While. . .

DETD By "irritable bowel syndrome" or "IBS" is intended any disorder associated with abdominal pain and/or abdominal discomfort and an alteration in bowel habit, and encompasses all symptoms including functional bowel, pylorospasm, nervous indigestion, spastic colon, spastic colitis, spastic bowel, intestinal neurosis, functional colitis, irritable colon, mucous colitis, laxative colitis, and functional dyspepsia.

DETD As used herein, the term "functional abdominal bloating" refers generally to a group of functional bowel disorders which are dominated by a feeling of abdominal fullness or bloating and without sufficient criteria for another functional gastrointestinal. . .

DETD . . . mucosal and structural abnormalities are present or there is evidence of a related metabolic disturbance that is not an inflammatory bowel disorder or an acid peptic disorder. Structural intestinal disorders include ulcers typically related to medications such as non-steroidal anti-inflammatory drugs,. . .

DETD . . . have evidence of a recent examination of the large intestine, with no evidence of other serious medical conditions including inflammatory bowel disease.

DETD . . . are three phases to the study. There is a 2-week screening period to confirm the symptomatology and record changes in bowel habit. Randomization of all subjects that continue to be eligible will be made after that 2-week period to a group.. . .

DETD The ability of MCI-225 to reverse acetic acid-induced colonic hypersensitivity in a rodent model of irritable bowel syndrome was assessed. Specifically, the experiments described herein investigated the effect of MCI-225 on visceromotor responses in a rat model. . .

CLM What is claimed is:
18. The method of claim 17, wherein the disorder is a functional bowel disorder, irritable bowel syndrome, irritable bowel syndrome with diarrhea, chronic functional vomiting, overactive bladder or a combination thereof.

IT 99487-26-0, MCI-225
(soluble salts of thienopyrimidine derivs., and therapeutic use)

L14 ANSWER 8 OF 20 IMSDRUGNEWS COPYRIGHT 2008 IMSWORLD on STN

AN 2006:1692 IMSDRUGNEWS
TI DDP 225 Dynogen phase change II, USA(emesis)
SO R&D Focus Drug News (27 Mar 2006).
WC 102
TX DDP . . . a noradrenaline reuptake inhibitor and 5HT3 receptor antagonist, is also undergoing phase II evaluation for the treatment of diarrhea-predominant irritable bowel syndrome (IBS). Dynogen acquired DDP 225 from Mitsubishi Pharma in December 2003, under a

Technology Transfer and License agreement to. . .
RN 135991-48-9

L14 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2008 ACS on STN
AN 2006:1030476 CAPLUS
DN 145:389426
TI Method of treating disorders and conditions using peripherally restricted 5-HT3 antagonists and inhibitors
IN Thor, Karl Bruce; Ricca, Daniel J.
PA Dynogen Pharmaceuticals, Inc., USA
SO PCT Int. Appl., 129pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2006105117	A2	20061005	WO 2006-US11334	20060327
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 20060293309	A1	20061228	US 2006-389887	20060327
PRAI US 2005-666253P	P	20050328		

OS MARPAT 145:389426
AB The invention features compds., e.g. 5-HT3 receptor antagonists, having a peripherally restricted mode of action such that the compds. affect 5-HT3 receptors of the peripheral nervous system with diminished or reduced effects in the central nervous system. The compds. are particularly useful in treating disorders or conditions ameliorated by antagonism of peripheral 5-HT3 receptors. Moreover, side-effects attributable to antagonism of central 5-HT3 receptors can be lessened or reduced using the peripherally restricted compds. of the invention. Compds. of the invention are quaternary ammonium derivs. of MCI-225. Compound preparation is included.
IT Intestine, disease
(constipation, alternating constipation/diarrhea irritable bowel syndrome; MCI-225 quaternary ammonium derivative peripherally restricted 5-HT3 antagonists for treatment of disorders and conditions)
IT Diarrhea
(diarrhea-predominant or alternating constipation/diarrhea irritable bowel syndrome; MCI-225 quaternary ammonium derivative peripherally restricted 5-HT3 antagonists for treatment of disorders and conditions)
IT Intestine, disease
(irritable bowel syndrome; MCI-225 quaternary ammonium derivative peripherally restricted 5-HT3 antagonists for treatment of disorders and conditions)
IT 99487-26-0D, MCI 225, quaternary ammonium derivs. 911197-71-2
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MCI-225 quaternary ammonium derivative peripherally restricted 5-HT3 antagonists for treatment of disorders and conditions)

L14 ANSWER 10 OF 20 USPATFULL on STN

AN 2006:341526 USPATFULL
TI Method of treating disorders and conditions using peripherally-restricted antagonists and inhibitors
IN Thor, Karl Bruce, Cary, NC, UNITED STATES
Ricca, Daniel J., Rougemont, NC, UNITED STATES
PA Dynogen Pharmaceuticals, Inc., Waltham, MA, UNITED STATES (U.S. corporation)
PI US 20060293309 A1 20061228
AI US 2006-389887 A1 20060327 (11)
PRAI US 2005-666253P 20050328 (60)
DT Utility
FS APPLICATION
LREP LAHIVE & COCKFIELD, LLP, ONE POST OFFICE SQUARE, BOSTON, MA, 02109-2127, US
CLMN Number of Claims: 101
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 4659
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The instant invention features compounds, for example, 5-HT.sub.3 receptor antagonists, having a peripherally restricted mode of action such that the compounds affect 5-HT.sub.3 receptors of the peripheral nervous system with diminished or reduced effects in the central nervous system. The compounds are particularly useful in treating disorders or conditions ameliorated by antagonism of peripheral 5-HT.sub.3 receptors. Moreover, side-effects attributable to antagonism of central 5-HT.sub.3 receptors can be lessened or reduced using the peripherally restricted compounds of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM In one embodiment, the 5-HT.sub.3 mediated disorder is a functional bowel disorder, e.g., irritable bowel syndrome (IBS). In an exemplary embodiment, the 5-HT.sub.3 mediated disorder is diarrhea-predominant irritable bowel syndrome (IBS-d). In another embodiment, the 5-HT.sub.3 mediated disorder is a lower urinary tract disorder, e.g., overactive bladder (OAB) including. . .
SUMM In one aspect, the invention relates to a method for treating a functional bowel disorder, e.g., at least one symptom of a functional bowel disorder, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a quaternary ammonium. . .
SUMM Another aspect of the invention relates to a method for treating a functional bowel disorder, e.g., at least one symptom of a functional bowel disorder, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of. . .
SUMM In another aspect, the invention is directed to a method for treating a functional bowel disorder, e.g., at least one symptom of a functional bowel disorder, in a subject in need thereof comprising coadministering to said subject a peripherally-restricted 5-HT.sub.3 receptor antagonist with an additional. . .
SUMM In another aspect, the invention is directed to a packaged pharmaceutical composition for treating a functional bowel disorder, e.g., at least one symptom of a functional bowel disorder, in a subject, comprising a container holding a therapeutically effective amount of a peripherally-restricted 5-HT.sub.3 receptor antagonist; and instructions for using the antagonist for treating a functional bowel disorder in a subject.
SUMM Another aspect of the invention pertains to a packaged pharmaceutical composition for treating a functional bowel disorder, e.g., at least one symptom of a functional bowel disorder, in a subject, comprising a container holding a therapeutically effective

amount of a peripherally-restricted 5-HT.sub.3 receptor antagonist; and instructions for using the antagonist and an additional agent for treating a functional bowel disorder in a subject.

SUMM . . . directed to a pharmaceutical composition comprising a peripherally-restricted 5-HT.sub.3 receptor antagonist and a pharmaceutically acceptable carrier for treating a functional bowel disorder, e.g., at least one symptom of a functional bowel disorder, in a subject, wherein the peripherally-restricted 5-HT.sub.3 receptor antagonist is selected based on its peripheral restriction, e.g., an MCI-225-QUAT.

SUMM . . . pharmaceutical composition comprising a peripherally-restricted 5-HT.sub.3 receptor antagonist, an additional agent and a pharmaceutically acceptable carrier for treating a functional bowel disorder in a subject.

DETD The invention relates to methods of treating vomiting, nausea, retching, lower urinary tract disorders, functional bowel disorders, and other 5-HT.sub.3 mediated disorders in a subject in need of treatment. The methods comprise administering to a subject. . .

DETD . . . of 5-HT.sub.3 receptors in a subject in need of treatment. In one embodiment, the 5-HT.sub.3 mediated disorder is a functional bowel disorder, e.g., irritable bowel syndrome (IBS). In an exemplary embodiment, the 5-HT.sub.3 mediated disorder is diarrhea-predominant irritable bowel syndrome (IBS-d). In another embodiment, the 5-HT.sub.3 mediated disorder is a lower urinary tract disorder, e.g., overactive bladder (OAB) including. . .

DETD For example, when the 5-HT.sub.3 mediated disorder is a functional bowel disorder, for example IBS, e.g., IBS-d, a reduction in the pain or discomfort associated with IBS, as well as the. . .

DETD . . . effective amount of a quaternary ammonium derivative of MCI-225 (MCI-225-QUAT). In one embodiment, the 5-HT.sub.3 mediated disorder is a functional bowel disorder, for example, IBS. In an exemplary embodiment, the 5-HT.sub.3 mediated disorder is diarrhea-predominant irritable bowel syndrome (IBS-d). In another embodiment, the 5-HT.sub.3 mediated disorder is a lower urinary tract disorder, e.g., overactive bladder (OAB) (e.g.,. . .

DETD In a particular embodiment, exemplary 5-HT.sub.3 mediated disorders may include, but are not limited to vomiting, nausea, retching, functional bowel disorders, IBS, diseases and disorders of the lower urinary tract, OAB, pain, or any combination thereof.

DETD A. Functional Bowel Disorders

DETD Functional Bowel Disorders (FBDs) are functional gastrointestinal disorders having symptoms attributable to the mid or lower gastrointestinal tract. FBDs can include, but are not limited to Irritable Bowel Syndrome (IBS), e.g., IBS-d, dyspepsia, functional abdominal bloating, functional constipation and functional diarrhea (see, for example, Thompson et al., Gut,. . .

DETD Consequently, another embodiment of the invention is a method for treating a functional bowel disorder in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a quaternary ammonium derivative of MCI-225 (MCI-225-QUAT). In a particular embodiment, the functional bowel disorder is diarrhea predominant irritable bowel syndrome (IBS-d). In another embodiment, the functional bowel disorder is alternating constipation/diarrhea irritable bowel syndrome. In yet another embodiment, the functional bowel disorder is nonconstipated irritable bowel syndrome.

DETD 1. Irritable Bowel Syndrome

DETD IBS comprises a group of functional bowel disorders in which abdominal discomfort or pain is associated with defecation or change in bowel habit and with features of disordered defecation. Due to a lack of readily identifiable structural or biochemical abnormalities in IBS,. . .

DETD As such, IBS is a functional bowel disorder in which abdominal pain or discomfort is associated with defecation or a change in bowel habit. Therefore, IBS has elements of an intestinal motility disorder, a visceral sensation disorder, and a central nervous disorder. While. . .

DETD Functional abdominal bloating comprises a group of functional bowel disorders which are dominated by a feeling of abdominal fullness or bloating, and without sufficient criteria for another functional gastrointestinal. . .

DETD . . . antagonist with an additional agent. In particular embodiments, the 5-HT.sub.3 mediated disorder is selected from the group consisting of functional bowel disorder, for example IBS, e.g. IBS-d, symptoms of a lower urinary tract disorder, nausea, vomiting, for example CFV, retching, overactive. . .

DETD In another aspect, the invention is directed to a method for treating a functional bowel disorder in a subject in need thereof comprising coadministering to said subject a peripherally-restricted 5-HT.sub.3 receptor antagonist with an additional. . .

DETD In particular embodiments, the 5-HT.sub.3 mediated disorder is selected from the group consisting of functional bowel disorder, for example, IBS, e.g., IBS-d, symptoms of a lower urinary tract disorder, nausea, vomiting, for example, CFV, retching, overactive. . .

DETD . . . directed to a pharmaceutical composition comprising a peripherally-restricted 5-HT.sub.3 receptor antagonist and a pharmaceutically acceptable carrier for treating a functional bowel disorder, for example, IBS, e.g., IBS-d, in a subject, wherein the peripherally-restricted 5-HT.sub.3 receptor antagonist is selected based on its. . .

DETD . . . pharmaceutical composition comprising a peripherally-restricted 5-HT.sub.3 receptor antagonist, an additional agent and a pharmaceutically acceptable carrier for treating a functional bowel disorder, for example, IBS, e.g., IBS-d, in a subject.

DETD In another embodiment, the invention is directed to a packaged pharmaceutical composition for treating a functional bowel disorder, e.g., IBS, e.g., IBS-d, in a subject, comprising a container holding a therapeutically effective amount of a peripherally-restricted 5-HT.sub.3 receptor antagonist; and instructions for using the antagonist for treating a functional bowel disorder in a subject.

DETD Another embodiment of the invention pertains to a packaged pharmaceutical composition for treating a functional bowel disorder, e.g., IBS, e.g., IBS-d, in a subject, comprising a container holding a therapeutically effective amount of a peripherally-restricted 5-HT.sub.3 receptor antagonist; and instructions for using the antagonist and an additional agent for treating a functional bowel disorder in a subject.

DETD Treatment of Functional Bowel Disease

DETD The ability of a test compound to reverse acetic acid-induced colonic hypersensitivity in a rodent model of irritable bowel syndrome is assessed. Specifically, the experiments described herein investigate the effect of a test compound on visceromotor responses in a. . .

CLM What is claimed is:

2. The method of claim 1, wherein the 5-HT3 mediated disorder is selected from the group consisting of functional bowel disorder, symptoms of a lower urinary tract disorder, nausea, vomiting, retching, overactive bladder (OAB), stress urinary incontinence, pain, fibromyalgia and. . .

CLM What is claimed is:

26. The method of claim 19, wherein the 5-HT.sub.3 mediated disorder is selected from the group consisting of functional bowel disorder, symptoms of a lower urinary tract disorder, nausea, vomiting, retching, overactive bladder (OAB), stress urinary incontinence, pain,

fibromyalgia and. . .

CLM What is claimed is:

. . . 33. The packaged pharmaceutical of claim 31, wherein the 5-HT.sub.3 mediated disorder is selected from the group consisting of functional bowel disorder, symptoms of a lower urinary tract disorder, nausea, vomiting, retching, overactive bladder (OAB), stress urinary incontinence, pain, fibromyalgia and. . .

CLM What is claimed is:

. . . 38. The pharmaceutical composition of claim 34, wherein the 5-HT.sub.3 mediated disorder is selected from the group consisting of functional bowel disorder, symptoms of a lower urinary tract disorder, nausea, vomiting, retching, overactive bladder (OAB), stress urinary incontinence, pain, fibromyalgia and. . .

CLM What is claimed is:

39. A method for treating a functional bowel disorder in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound selected. . . ammonium derivative of MCI-225 (MCI-225-QUAT); (b) a peripherally-restricted 5-HT.sub.3 receptor antagonist together with an additional agent for treating the functional bowel disorder in the subject; and (c) a peripherally-restricted 5-HT.sub.3 receptor antagonist together with a noradrenaline reuptake inhibitor.

CLM What is claimed is:

40. The method of claim 39, wherein the functional bowel disorder is selected from the group consisting of (a) irritable bowel syndrome, (b) diarrhea-predominant irritable bowel syndrome, (c) alternating constipation/diarrhea irritable bowel syndrome, and (d) nonconstipated irritable bowel syndrome.

CLM What is claimed is:

60. A method for treating a functional bowel disorder in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound selected. . .

CLM What is claimed is:

167. A packaged pharmaceutical composition for treating a functional bowel disorder in a subject, comprising a container holding a therapeutically effective amount of a peripherally-restricted 5-HT.sub.3 receptor antagonist; and instructions for using the composition for treating the functional bowel disorder in the subject.

CLM What is claimed is:

168. The packaged pharmaceutical composition of claim 167 further comprising an additional agent for treating the functional bowel disorder in the subject.

CLM What is claimed is:

169. A pharmaceutical composition for treating a functional bowel disorder in a subject, comprising a compound selected from the group consisting of: (a) a peripherally-restricted 5-HT.sub.3 receptor antagonist selected. . . an enhanced therapeutic profile; and (d) a peripherally-restricted 5-HT.sub.3 receptor antagonist together with an additional agent for treating the functional bowel disorder in the subject; and a pharmaceutically acceptable carrier.

CLM What is claimed is:

173. The pharmaceutical composition of claim 169, wherein the functional bowel disorder is selected from the group consisting of (a) irritable bowel syndrome, (b) diarrhea-predominant irritable bowel syndrome, (c) alternating constipation/diarrhea irritable bowel syndrome, and (d) nonconstipated irritable bowel

syndrome.

IT 99487-26-0D, MCI 225, quaternary ammonium derivs. 911197-71-2
(MCI-225 quaternary ammonium derivative peripherally restricted 5-HT3 antagonists for treatment of disorders and conditions)

L14 ANSWER 11 OF 20 IMSDRUGNEWS COPYRIGHT 2008 IMSWORLD on STN

AN 2005:2868 IMSDRUGNEWS
TI DDP 225 Dynogen initiates clinical trials (irritable bowel syndrome)
SO R&D Focus Drug News (9 May 2005).
WC 45
TI DDP 225 Dynogen initiates clinical trials (irritable bowel syndrome)
TX Dynogen . . . initiated clinical trials with the thienopyrimide analogue, DDP 225 (AA 10021;MCI 225) in the USA for the treatment of irritable bowel syndrome (IBS). Dynogen has a Technology Transfer agreement with Mitsubishi Pharma for the development of DDP 225 in the treatment. . .
RN 135991-48-9

L14 ANSWER 12 OF 20 USPATFULL on STN DUPLICATE 2
AN 2005:31472 USPATFULL
TI Method of treating lower urinary tract disorders
IN Landau, Steven B., Wellesley, MA, UNITED STATES
Miller, Cheryl L., Natick, MA, UNITED STATES
Fraser, Matthew O., Apex, NC, UNITED STATES
PA Dynogen, Inc. (U.S. corporation)
PI US 20050026909 A1 20050203
US 7115606 B2 20061003
AI US 2004-863770 A1 20040607 (10)
RLI Continuation of Ser. No. US 2004-817332, filed on 2 Apr 2004, PENDING
PRAI US 2004-536341P 20040113 (60)
US 2003-496502P 20030820 (60)
US 2003-461022P 20030404 (60)
DT Utility
FS APPLICATION
LREP JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017
CLMN Number of Claims: 49
ECL Exemplary Claim: CLM-01-70
DRWN 2 Drawing Page(s)
LN.CNT 3245
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis. The method comprises administering to a subject in need of treatment a therapeutically effective amount of a compound that has 5-HT.sub.3 receptor antagonist activity and NorAdrenaline Reuptake Inhibitor (NARI) activity. The invention further relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis, comprising coadministering to said subject a first amount of a 5-HT.sub.3 antagonist and a second amount of a NARI, wherein the first and second amounts together comprise a therapeutically effective amount or are each present in a therapeutically effective amount.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . under a health insurance policy submitted by a claimant seeking

reimbursement for costs associated with the treatment of a functional bowel disorder as described herein.

IT 99487-26-0, MCI-225
(as 5-HT3 antagonist and noradrenaline reuptake inhibitor; 5-HT3 receptor antagonist and noradrenaline reuptake inhibitor combination for treating lower urinary tract disorders)

L14 ANSWER 13 OF 20 USPATFULL on STN
AN 2005:324887 USPATFULL
TI Method of treating lower urinary tract disorders
IN Landau, Steven B., Wellesley, MA, UNITED STATES
Miller, Cheryl L., Natick, MA, UNITED STATES
Fraser, Matthew O., Apex, NC, UNITED STATES
PA Dynogen, Inc. (U.S. corporation)
PI US 20050282799 A1 20051222
AI US 2005-124580 A1 20050506 (11)
RLI Continuation of Ser. No. US 2004-863771, filed on 7 Jun 2004, PENDING
Continuation of Ser. No. US 2004-817332, filed on 2 Apr 2004, GRANTED, Pat. No. US 6846823
PRAI US 2004-536341P 20040113 (60)
US 2003-496502P 20030820 (60)
US 2003-461022P 20030404 (60)
DT Utility
FS APPLICATION
LREP JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017, US
CLMN Number of Claims: 7
ECL Exemplary Claim: 1-70
DRWN 2 Drawing Page(s)
LN.CNT 3128
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis. The method comprises administering to a subject in need of treatment a therapeutically effective amount of a compound that has 5-HT.sub.3 receptor antagonist activity and NorAdrenaline Reuptake Inhibitor (NARI) activity. The invention further relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis, comprising coadministering to said subject a first amount of a 5-HT.sub.3 antagonist and a second amount of a NARI, wherein the first and second amounts together comprise a therapeutically effective amount or are each present in a therapeutically effective amount.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . under a health insurance policy submitted by a claimant seeking reimbursement for costs associated with the treatment of a functional bowel disorder as described herein.
IT 99487-26-0, MCI-225
(as 5-HT3 antagonist and noradrenaline reuptake inhibitor; 5-HT3 receptor antagonist and noradrenaline reuptake inhibitor combination for treating lower urinary tract disorders)

L14 ANSWER 14 OF 20 USPATFULL on STN
AN 2005:313100 USPATFULL
TI Method for inhibiting detrusor muscle overactivity
IN Landau, Steven B., Wellesley, MA, UNITED STATES
Miller, Cheryl L., Natick, MA, UNITED STATES
Fraser, Matthew O., Apex, NC, UNITED STATES
PI US 20050272719 A1 20051208

AI US 2005-122940 A1 20050504 (11)
RLI Continuation of Ser. No. US 2004-863771, filed on 7 Jun 2004, PENDING
Continuation of Ser. No. US 2004-817332, filed on 2 Apr 2004, GRANTED, Pat. No. US 6846823
PRAI US 2004-536341P 20040113 (60)
US 2003-496502P 20030820 (60)
US 2003-461022P 20030404 (60)
DT Utility
FS APPLICATION
LREP JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017, US
CLMN Number of Claims: 37
ECL Exemplary Claim: 1-70
DRWN 2 Drawing Page(s)
LN.CNT 3180
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis. The method comprises administering to a subject in need of treatment a therapeutically effective amount of a compound that has 5-HT.sub.3 receptor antagonist activity and NorAdrenaline Reuptake Inhibitor (NARI) activity. The invention further relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis, comprising coadministering to said subject a first amount of a 5-HT.sub.3 antagonist and a second amount of a NARI, wherein the first and second amounts together comprise a therapeutically effective amount or are each present in a therapeutically effective amount.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . under a health insurance policy submitted by a claimant seeking reimbursement for costs associated with the treatment of a functional bowel disorder as described herein.
IT 99487-26-0, MCI-225
(as 5-HT3 antagonist and noradrenaline reuptake inhibitor; 5-HT3 receptor antagonist and noradrenaline reuptake inhibitor combination for treating lower urinary tract disorders)

L14 ANSWER 15 OF 20 USPATFULL on STN
AN 2005:275228 USPATFULL
TI 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine in the treatment of functional bowel disorder
IN Cavalla, David, Cambridge, UNITED KINGDOM
Gristwood, Robert William, Cambridge, UNITED KINGDOM
PI US 20050239792 A1 20051027
AI US 2003-519594 A1 20030709 (10)
WO 2003-GB2974 20030709
20041228 PCT 371 date
PRAI GB 2002-16027 20020710
DT Utility
FS APPLICATION
LREP SALIWANCHIK LLOYD & SALIWANCHIK, A PROFESSIONAL ASSOCIATION, PO BOX 142950, GAINESVILLE, FL, 32614-2950, US
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 160
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Use of 4-(2-Fluorophenyl)-6-Methyl-2-(1-Piperazinyl)Thieno[2,3-D]Pyrimidine or a salt thereof for the manufacture of a medicament for

the treatment of functional bowel disorder.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d)pyrimidine in the treatment of functional bowel disorder
AB Use of 4-(2-Fluorophenyl)-6-Methyl-2-(1-Piperazinyl)Thieno[2,3-D]Pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of functional bowel disorder.
SUMM Functional bowel disorders are very common and include irritable bowel syndrome (IBS) and functional dyspepsia. IBS is the most common disorder diagnosed by gastroenterologists and one of the more common. . . .
SUMM . . . been found that the known compound identified above (referred to herein as MCI-225) has activity in the treatment of functional bowel disorders. Its combination of serotonin and noradrenergic reuptake blockade and 5HT-3 receptor blockade has not previously been clearly identified as being responsible for activity in functional bowel disorders. Furthermore MCI-225, at doses effective in the treatment of bowel disorders, can produce a lower incidence of some of the side-effects which are commonly known to be associated with the. . .
DETD By means of this invention, functional bowel disorders and associated pain symptoms can be treated, e.g. controlled or prevented. Such disorders include irritable bowel syndrome, including diarrhoea-predominant, constipation-predominant, and alternating constipation/diarrhoea IBS. The patient may be male or female, diarrhoea-predominant IBS being particularly associated. . .
DETD . . . an inhibition of the reflex indicates modulation of visceral nociceptive neurotransmission and, therefore, the use of the drug in functional bowel disease (e.g. IBS); see Kozlowski et al, 2000, Gut 46, 474-480. Allodynia and visceral pain are important components of functional bowel disease.
CLM What is claimed is:
1. A method for the treatment of a functional bowel disorder wherein said method comprises administering, to a patient in need of such treatment, an effective amount of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D}pyrimidine or. . .
CLM What is claimed is:
3. The method, according to claim 1, wherein the disorder is irritable bowel syndrome.

CLM What is claimed is:
4. The method, according to claim 3, wherein the disorder is diarrhea-predominant irritable bowel syndrome.

CLM What is claimed is:
6. The method, according to claim 3, wherein the disorder is alternating constipation/diarrhea irritable bowel syndrome.

CLM What is claimed is:
7. The method, according to claim 3, wherein the disorder is constipation-predominant irritable bowel syndrome.

IT 99487-25-9 99487-26-0, MCI 225 476148-82-0
(thienopyrimidine deriv.for treatment of pain)

L14 ANSWER 16 OF 20 USPATFULL on STN
AN 2005:24028 USPATFULL
TI Method of treating lower urinary tract disorders
IN Landau, Steven B., Wellesley, MA, UNITED STATES
Miller, Cheryl L., Natick, MA, UNITED STATES
Fraser, Matthew O., Apex, NC, UNITED STATES

PA Dynogen, Inc. (U.S. corporation)
PI US 20050020577 A1 20050127
AI US 2004-863771 A1 20040607 (10)
RLI Continuation of Ser. No. US 2004-817332, filed on 2 Apr 2004, PENDING
PRAI US 2004-536341P 20040113 (60)
US 2003-496502P 20030820 (60)
US 2003-461022P 20030404 (60)
DT Utility
FS APPLICATION
LREP JONES DAY, 222 EAST 41ST ST, NEW YORK, NY, 10017
CLMN Number of Claims: 27
ECL Exemplary Claim: CLM-01-70
DRWN 2 Drawing Page(s)
LN.CNT 3306
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis. The method comprises administering to a subject in need of treatment a therapeutically effective amount of a compound that has 5-HT.sub.3 receptor antagonist activity and NorAdrenaline Reuptake Inhibitor (NARI) activity. The invention further relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis, comprising coadministering to said subject a first amount of a 5-HT.sub.3 antagonist and a second amount of a NARI, wherein the first and second amounts together comprise a therapeutically effective amount or are each present in a therapeutically effective amount.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . under a health insurance policy submitted by a claimant seeking reimbursement for costs associated with the treatment of a functional bowel disorder as described herein.
IT 99487-26-0, MCI-225
(as 5-HT3 antagonist and noradrenaline reuptake inhibitor; 5-HT3 receptor antagonist and noradrenaline reuptake inhibitor combination for treating lower urinary tract disorders)

L14 ANSWER 17 OF 20 IMSDRUGNEWS COPYRIGHT 2008 IMSWORLD on STN

AN 2004:188 IMSDRUGNEWS
TI DDP 225 Dynogen, Mitsubishi Pharma licensing agreement
SO R&D Focus Drug News (12 Jan 2004).
WC 143
TX Dynogen . . . Transfer and License agreement with Mitsubishi Pharma regarding development of DDP 225 (formerly MCI 225) in the treatment of irritable bowel syndrome. The agreement grants Dynogen rights to all clinical trial data and other information for research, development and manufacturing of. . .

DDP . . . Japan in the treatment of depression. Dynogen has filed broad patent applications covering the use of the compound for irritable bowel syndrome and certain other genitourinary and gastrointestinal indications. Dynogen plans to begin phase II trials of DDP 225 during 2004.
RN 135991-48-9
RN 135991-48-9

L14 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2008 ACS on STN DUPLICATE 3
AN 2004:203555 CAPLUS

DN 140:229465
TI New therapeutic use of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-d]pyrimidine
IN Bardsley, Hazel Judith; Cavalla, David; Gristwood, Robert William
PA Germany
SO U.S. Pat. Appl. Publ., 4 pp., Cont.-in-part of Appl. No. PCT/GB2002/02388.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 20040048874	A1	20040311	US 2003-617847	20030710
	WO 2002094249	A1	20021128	WO 2002-GB2388	20020521
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	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
	AU 2005200045	A1	20050127	AU 2005-200045	20050107
	AU 2007202664	A1	20070712	AU 2007-202664	20070614
PRAI	GB 2001-12494	A	20010522		
	WO 2002-GB2388	A2	20020521		
	GB 2002-16027	A	20020710		
	AU 2002-307872	A3	20020521		
	AU 2003-255712	A3	20030709		

AB 4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof is useful for the treatment of pain.
ST fluorophenylmethylpiperazinylthienopyrimidine analgesic pain fibromyalgia irritable bowel syndrome diarrhea constipation
IT Intestine, disease
(irritable bowel syndrome, constipation-predominant; fluorophenylmethylpiperazinylthienopyrimidine for treatment of pain)
IT Intestine, disease
(irritable bowel syndrome; fluorophenylmethylpiperazinylthien opyrimidine for treatment of pain)
IT 53-86-1, Indomethacin 99487-25-9 99487-26-0, MCI-225 476148-82-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(fluorophenylmethylpiperazinylthienopyrimidine for treatment of pain)

L14 ANSWER 19 OF 20 USPATFULL on STN DUPLICATE 4
AN 2004:268326 USPATFULL
TI Method of treating lower urinary tract disorders
IN Landau, Steven B., Wellesley, MA, UNITED STATES
Miller, Cheryl L., Natick, MA, UNITED STATES
Fraser, Mathew O., Apex, NC, UNITED STATES
PA Dynogen Pharmaceuticals, Inc., Boston, MA (U.S. corporation)

PI	US 20040209869	A1	20041021
	US 6846823	B2	20050125
AI	US 2004-817332	A1	20040402 (10)
PRAI	US 2004-536341P		20040113 (60)
	US 2003-496502P		20030820 (60)
	US 2003-461022P		20030404 (60)

DT Utility
FS APPLICATION
LREP HAMILTON, BROOK, SMITH & REYNOLDS, P.C., 530 VIRGINIA ROAD, P.O. BOX

9133, CONCORD, MA, 01742-9133
CLMN Number of Claims: 70
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 3437
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis. The method comprises administering to a subject in need of treatment a therapeutically effective amount of a compound that has 5-HT.sub.3 receptor antagonist activity and NorAdrenaline Reuptake Inhibitor (NARI) activity. The invention further relates to a method of treating at least one symptom of a lower urinary tract disorder in a subject in need of treatment wherein the symptom is selected from the group consisting of urinary frequency, urinary urgency, urinary urge incontinence, nocturia and enuresis, comprising coadministering to said subject a first amount of a 5-HT.sub.3 antagonist and a second amount of a NARI, wherein the first and second amounts together comprise a therapeutically effective amount or are each present in a therapeutically effective amount.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . under a health insurance policy submitted by a claimant seeking reimbursement for costs associated with the treatment of a functional bowel disorder as described herein.
IT 99487-26-0, MCI-225
(as 5-HT3 antagonist and noradrenaline reuptake inhibitor; 5-HT3 receptor antagonist and noradrenaline reuptake inhibitor combination for treating lower urinary tract disorders)

L14 ANSWER 20 OF 20 ADISINSIGHT COPYRIGHT (C) 2008 Adis Data Information BV on STN
RN 99487-26-0
CC. . . CODE: A4 Antiemetics and Antinauseants; A7E Intestinal Anti-Inflammatory Agents; G4 Urologicals; N6A Anti-Depressants and Mood Stabilisers
CC WHO ATC CODE: A03A Drugs for Functional Bowel Disorders; A04 Antiemetics and Antinauseants; G04 Urologicals; N06A Antidepressants
DSTA Phase II, Canada, Irritable bowel syndrome
Phase II, United States, Irritable bowel syndrome
Phase I, North America, Overactive bladder
Discontinued III, Japan, Depression
Discontinued II, United States, Nausea and vomiting

TX TEXT
Introduction:
Dynogen Pharmaceuticals is developing DDP 225, a thienopyrimidine analogue, for the oral treatment of iritable bowel syndrome (IBS) and overactive bladder (OAB). DDP 225 is a noradrenaline reuptake inhibitor (NARI) and serotonin sub(3) (5-HT sub(3)) receptor. . . and serotonin is thought to play an important role in a number of gastrointestinal and genitourinary disorders such as irritable bowel syndrome (IBS) and overactive bladder (OAB). It is believed that noradrenaline is involved in pain sensation, while serotonin has been. . . Mitsubishi Pharma Corporation for DDP 225 (formerly MCI 225), whereby Dynogen will develop the compound for the treatment of irritable bowel syndrome (IBS). The agreement provides Dynogen with rights to all clinical trial data and other information useful for the research,. . . drug material adequate to complete Dynogen's phase II clinical trials. Financial terms were not disclosed/1/.

Key development milestones
Irritable bowel syndrome: DDP 225 is undergoing phase II trials with Dynogen for the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-d). In October 2005, Dynogen initiated a phase IIa proof-of-concept study (NCT00230581) of DDP 225 in the IBS-d indication. . . Arachnova to Dynogen included patents and pending applications related to the use of DDP 225 for the treatment of functional bowel disorders, genitourinary disorders and pain. These patents are expected to complement and enhance the existing patent estate held by Dynogen/6/.
. . .
. . . was reported to be generally well tolerated and safe after analysis of a phase IIa trial in patients with irritible bowel syndrome with diarrhoea. There were no serious or severe adverse events or any that resulted in discontinuation of treatment/9/.
Animal. . .
. . . TRIALS:
Digestive System Disorders:
In a phase II study, DDP 225 showed positive results for the treatment of patients with irritable bowel syndrome (IBS) with diarrhoea. A total of 87 female patients were enrolled at multiple centres across the US and Canada;. . .

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=> d l14 bib abs 20
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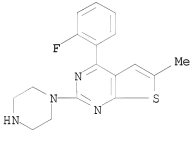
L14 ANSWER 20 OF 20 ADISINSIGHT COPYRIGHT (C) 2008 Adis Data Information BV
     on STN
AN   1998:1266 ADISINSIGHT
SO   Adis R&D Insight
DN   001419
CDAT May 23, 2008
CN   DDP 225
CN   4-(2-Fluorophenyl)-6-methyl-2-piperazinothieno (2,3-d)pyrimidine
     hydrochloride hydrate
MF   C17 H17 F N4 S . H Cl . H2 O
RN   99487-26-0
STR



● HCl

CC   EPHMRA ATC CODE: A4 Antiemetics and Antinauseants; A7E Intestinal
     Anti-Inflammatory Agents; G4 Urologicals; N6A Anti-Depressants and Mood
     Stabilisers
CC   WHO ATC CODE: A03A Drugs for Functional Bowel Disorders; A04
     Antiemetics and Antinauseants; G04 Urologicals; N06A Antidepressants
HDP Phase II
DSTA Phase II, Canada, Irritable bowel syndrome
     Phase II, United States, Irritable bowel syndrome
     Phase I, North America, Overactive bladder
     Discontinued III, Japan, Depression
     Discontinued II, United States, Nausea and vomiting
ORIGINATOR: Mitsubishi Chemical (Japan)
PARENT: Mitsubishi Chemical
LICENSEE: Dynogen Pharmaceuticals

OTHER: Mitsubishi Tanabe Pharma Corporation
OS 809055486; 809083639
WC 976

TX TEXT

Introduction:

Dynogen Pharmaceuticals is developing DDP 225, a thienopyrimidine analogue, for the oral treatment of iritable bowel syndrome (IBS) and overactive bladder (OAB). DDP 225 is a noradrenaline reuptake inhibitor (NARI) and serotonin sub(3) (5-HT sub(3)) receptor antagonist that was initially identified by Mitsubishi Chemical. Mitsubishi Tanabe Pharma Corporation (formerly Mitsubishi Pharma Corporation) has gained the rights to the compound. The activity of neurotransmitters such as noradrenaline and serotonin is thought to play an important role in a number of gastrointestinal and genitourinary disorders such as irritable bowel syndrome (IBS) and overactive bladder (OAB). It is believed that noradrenaline is involved in pain sensation, while serotonin has been linked to regulation of gastrointestinal motility. Clinical development of DDP 225 for the treatment of IBS and OAB is underway.

DDP 225 was also being developed for depression and nausea and vomiting, but development was discontinued for these indications. The agent was previously known as MCI 225.

MCI 225 is in development with Arachnova Therapeutics for a variety of indications (see the separate profile for MCI 225).

Company agreements

In October 2003, Dynogen Pharmaceuticals, Inc. entered into a Technology Transfer and Licence agreement with Mitsubishi Pharma Corporation for DDP 225 (formerly MCI 225), whereby Dynogen will develop the compound for the treatment of irritable bowel syndrome (IBS). The agreement provides Dynogen with rights to all clinical trial data and other information useful for the research, development and manufacturing of the compound, as well as a supply of drug material adequate to complete Dynogen's phase II clinical trials. Financial terms were not disclosed/1/.

Key development milestones

Irritable bowel syndrome: DDP 225 is undergoing phase II trials with Dynogen for the treatment of diarrhoea-predominant irritable bowel syndrome (IBS-d). In October 2005, Dynogen initiated a phase IIa proof-of-concept study (NCT00230581) of DDP 225 in the IBS-d indication in the US and Canada; the trial was completed in 2007/2/ /3/. Dynogen released positive results of the phase IIa trial in December 2007/4/. A phase IIb trial in IBS-d is scheduled for 2008.

Nausea and vomiting: Dynogen initiated a US-based phase II trial of DDP 225 in patients with chronic functional vomiting in March 2006/5/. However, the trial was later terminated. Development in this indication appears to have been discontinued, as the Dynogen product pipeline in the fourth quarter of 2007 did not mention this indication.

Overactive bladder (OAB): a phase Ib trial of DDP 225 for OAB has been completed, according to the Dynogen product pipeline in the fourth quarter of 2007. The trial location appears to have been in North America. Dynogen is preparing for a phase II trial in this indication.

Depression: MCI 225 was undergoing development in Japan as an antidepressant. Mitsubishi Chemical was collaborating with Taisho Pharmaceutical on phase III clinical testing of this compound. However, development of the compound in this indication was discontinued.

Patent information
Dynogen acquired patent rights and know-how relating to DDP 255 through an asset purchase agreement established with Arachnova Therapeutics in January 2008. The intellectual propery transfered from Arachnova to Dynogen included patents and pending applications related to the use of DDP 225 for the treatment of functional bowel disorders, genitourinary disorders and pain. These patents are expected to complement and enhance the existing patent estate held by Dynogen/6/.

Dynogen Pharmaceuticals was awarded US Patent No. 6 846 823 (the '823 patent) in January 2005, which relates to the use of DDP 225 for the treatment of lower urinary tract disorders. This patent covers the use of a broad class of thieno(2,3-d)pyrimidine derivatives, including DDP 225, for the treatment of urinary frequency, urinary urgency, nocturia and enuresis (bedwetting). These symptoms are associated with OAB, the irritative symptoms of benign prostatic hyperplasia (BPH), interstitial cystitis and other lower urinary tract disorders. Additionally, this patent also protects the mechanism of action by covering the use of any 5-HT3 receptor antagonist in combination with any noradrenaline reuptake inhibitor (NARI) for the treatment of frequency, urgency, nocturia and enuresis/7/. In addition, Dynogen was granted US Patent No. 7 115 606 which claims the use of DDP 225 for the treatment of OAB in patients who are not incontinent/8/.

TX EVALUATION:
Depression 52 (PO).

TX PHARMACOLOGY OVERVIEW:
Pharmacodynamics:
Antidepressant activity
Mechanism of action:
Serotonin 3 receptor antagonists
Serotonin receptor antagonists
Biogenic amine receptor antagonists
G protein-coupled receptor antagonists
Serotonin receptor modulators
Neurotransmitter agents
Neurotransmitter receptor antagonists
Cell surface receptor antagonists
G protein-coupled receptor modulators
Biogenic amine receptor modulators
Membrane protein receptor antagonists
Membrane protein inhibitors
Cell surface receptor modulators
Protein inhibitors
Membrane protein modulators
Protein modulators
Norepinephrine reuptake inhibitors
Monoamine uptake inhibitors
Neurotransmitter agonists
Neurotransmitter modulators
Activity versus parent drug: unspecified parent

TX CLINICAL OVERVIEW:
Route(s) of Administration: PO
Administration Freq.(per day):
Drug Interactions:
Unknown.

TX Adverse Events:
Adverse events: DDP 225 was reported to be generally well tolerated and safe after analysis of a phase IIa trial in patients with irritible

bowel syndrome with diarrhoea. There were no serious or severe adverse events or any that resulted in discontinuation of treatment/9/.
Animal toxicology: in contrast with imipramine, MCI 225 100 mg/kg PO did not inhibit oxotremorine-induced tremor, salivation or lacrimation in mice, suggesting that MCI 225 did not have central or peripheral anticholinergic effects/10/.

TX PHARMACOLOGY:
Pharmacokinetics:

Pharmacodynamics (Affective Disorders):
MCI 225 inhibited the uptake of norepinephrine in rat brain cortical and hypothalamic synaptosomes as potently as maprotiline and imipramine. MCI 225 had potent affinity for the serotonin sub(3) receptor, where it is thought to have an antagonistic action/10/.
Single administration of MCI 225 10-100 mg/kg PO dose-dependently reduced the duration of immobility of rats in the forced swimming test. The minimum effective doses of MCI 225, maprotiline, imipramine and trazodone after repeated administration for 5 days were 1, 30, 10 and 30 mg/kg, respectively. Only MCI 225 had realised its full potential after this short treatment period. MCI 225 10-100 mg/kg did not change spontaneous motor activity/10/.

TX THERAPEUTIC TRIALS:
Digestive System Disorders:
In a phase II study, DDP 225 showed positive results for the treatment of patients with irritable bowel syndrome (IBS) with diarrhoea. A total of 87 female patients were enrolled at multiple centres across the US and Canada; patients were randomised to receive DDP 225 or placebo. DDP 225, administered at a dose of 1 mg/day for 8 weeks, was associated with a significantly (p = 0.009) greater response than placebo regarding the adequate relief of IBS pain or discomfort (71% vs 25%)/4/.

RDAT	RNTE
11 Oct 2002	Discontinued - Phase-III for Depression in Japan (unspecified route)
16 Mar 2000	Phase-III clinical trials for Depression in Japan (Unknown route)
25 Jan 1999	Mitsubishi Chemical will collaborate with Taisho Pharmaceutical on phase III clinical testing of MCI 22
12 Feb 1998	A preclinical study has been added to the pharmacodynamics and adverse events sections (631404)
09 Jan 1997	Phase-II clinical trials for Depression in Japan (Unknown route)
20 Apr 1995	New profile

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